Remarks

With the above amendments, claim 16 has been canceled, claims 1 and 10 have been amended, claims 18 and 19 have been added, and claims 1-15 and 17-19 are pending and ready for further action on the merits. No new matter has been incorporated. Support for new claims 18 and 19 may be found on page 9, first full paragraph. The amendment to claim 1 has support on page 20, lines 20-22 and the amendment to claim 10 comes from claim 16.

Rejections under 35 USC §112, second paragraph

In the Advisory Action that issued on March 15, 2001, the Examiner indicated that if the amendment to claim 1 were entered that claim 1 likely would be rejected under 35 USC §112, second paragraph as being indefinite as it is unclear to the Examiner what the units are on the phrase inactivation factor > 10^4.

As a point of clarification, because this factor is a ratio, the dimensions are unit-less. The virus inactivation factor was calculated as the ratio of the virus titer in the absence of an inactivating agent of the invention as control and the virus titer of the agent treated sample. Virus titer is defined as the number of infectious virus particles per ml of sample. The titration was performed by standard microtitration assays either microscopically or spectrophotometrically using a tetrazolium dye assay. It follows that for an inactivation factor of >10^4 that

there are more than 10^4 times fewer infected virus particles in the treated sample than in the untreated sample ("baseline"). Because it is believed that this ratio is no longer indefinite, it is respectfully submitted that the putative rejection should not be made.

Rejections under 35 USC §112, first and second paragraph

The Examiner maintains the rejection of claims 1-10 and newly rejects claims 13-16 under 35 U.S.C. §112, first paragraph for lack of enablement. More specifically, the Examiner asserts that the specification is not enabled for inactivating viruses in cell cultures by contacting the compositions with cyclic lipopeptides in concentrations greater than 70μM. The Examiner relies on a teaching of Vollenbroich et al. that the cyclic lipopeptide, surfactin, is lethal at concentrations greater than 70 μM. Claim 1 has been amended to be drawn to non-cell culture biological products. As such, the present invention as encompassed by claim 1 and dependent claims thereon is no longer drawn to inactivating viruses in cell cultures with concentrations of cyclic lipopeptides greater than 70μM. Withdrawal of the rejection is, therefore, respectfully requested.

Further, in the Advisory Action that issued March 15, 2001, the Examiner indicates that claim 10 would still be rejected under 35 USC §112, first and/or second paragraph for a failure to recite

a well defined family of immunodeficiency viruses, even in view of the above arguments. Claim 10 has been amended to incorporate the immunodeficiency viruses of claim 16 into it. It is believed that a well-defined family is now enumerated. Withdrawal of the rejection with respect to this claim is respectfully requested.

Rejections under 35 USC §103(a)

The Examiner maintains the rejection of claims 1, 3, 4-7, 9 and 10 and newly rejects claims 14-17 under 35 U.S.C. §103 as being obvious over Itokawa et al. The Examiner indicates that the arguments of September 9, 2000 are insufficient because the claims do not recite a degree of viral inactivation that must be achieved. Claim 1, and all dependent claims thereon, have been amended to recite that the degree of viral activation achieved using the claimed method is an inactivation factor > 10^4. This amendment is supported by page 8, paragraph 3 of the specification. Itokawa et al. disclose only a moderate amount of anti-HIV-1 activity and there is no disclosure in Itokawa et al. of inactivation by a factor of > 10^4. An inactivation factor of > 10^4 is considered to be indicative of a strong level of inactivation. For example, as demonstrated in Example 5 of the specification, after 60 minutes, no infectious particles could be found.

The Examiner asserts that the teaching by Itokawa et al. of a moderate amount of inactivation points directly to the use of cyclic peptides. However, this assertion is hindsight reconstruction of the invention. At the time of Itokawa et al. thousands of compounds had been identified which had "moderate" viral inactivation activity at least to the degree, or even somewhat better than that, of Itokawa et al. No reason has been presented by the Examiner to select the compounds of Itokawa et al. over the compounds of any other reference. There is no suggestion in Itokawa et al. that one would be able to achieve the degree of activation in the short time recited with the present invention. As such, the present invention is neither taught nor suggested by Itokawa et al. and withdrawal of the rejection is respectfully requested.

The Examiner further maintains the rejection claims 1, 3, 9 and 10 under 35 U.S.C. §103 as being obvious over Naruse et al. In response to the arguments of September 9, 2000, the Examiner asserts that Naruse et al. teaches an incubation of 72 hours to allow sufficient time for the formation of CPE as an indicator of HSV viability/inactivation not as the length of time required for virus inactivation. The Examiner further notes that the argument that pumilacidins are different than surfactins is insufficient because the claims are not limited to surfactins. Applicants

traverse this rejection and withdrawal thereof is respectfully requested.

A virus is a non-cellular entity that can only reproduce within a host cell. A characteristic of viruses is that the replication cycle (making copies of DNA or RNA) take place inside the host cell. Viruses consist of nucleic acid covered by protein. The virus uses the synthetic capabilities of the host cell to make progeny virus particles.

Viruses may be inactivated in two ways, a) indirectly or b) directly. An example of indirect viral inactivation is the treatment of virus-infected cells with an agent such as AZT (3'-azido-3'-deoxythymidine), which is a classical AIDS drug. AZT works by preventing insertion of the genetic material (RNA) of human immunodeficiency virus into the host genetic material (DNA), thus blocking viral replication. With indirect viral inactivation, the agent (AZT) stops the virus from multiplying, but does not actually "kill" the virus.

In contrast, with direct viral inactivation, the virus is actually killed. The agent attacks the viral membrane, for example, and kills the virus by disintegrating it. The present method is a direct method of inactivating viruses.

Naruse et al., on the other hand, disclose a method of indirect viral inactivation because with the method of Naruse et al. the host cell-dependent replication of the viral genetic

material is being targeted and affected. With the method of Naruse et al. viral growth and multiplication is being inhibited. Naruse et al. indicate on pages 274-275, regarding "Antiviral Activity,"

> Aliquots (50 µl each) of medium containing various concentrations of the test compounds were poured into wells of a 96-well microplate and 200 µl of the cell suspension...was added. To each well...virus was added.

With the method of Naruse et al. in the first step the test compound (e.g. pumilacidin) was added to the cells. In the second step virus was added to the test compound-treated cells. Naruse et al. further state on page 275, paragraph 1, that "Acyclovir was used as the reference compound in the assay." Acyclovir is an antiviral compound that is used to treat herpes virus through the indirect activation of the virus, by inhibiting synthesis of viral genetic material in host cells, similarly to the action of AZT with retroviruses. Acyclovir acts by inhibiting reverse transcriptase in the host cell. Thus, the method of Naruse et al. is an indirect method of viral inactivation that does not work by "killing" the viruses.

As noted above, the present method is directed to a method of directly inactivating viruses by killing them. The present method attacks the virus, completely independently of the host cell and the replication cycle of the virus in the host cell. There is no suggestion in Naruse et al. of a method of directly inactivating viruses.

Moreover, in the Advisory Action that issued March 15, 2001, the Examiner has asserted that the feature upon which the Applicants rely is not present in claim 1, this feature being direct inactivation of viruses. This element has now been added to claim 1. Accordingly, the present invention is not obvious over Naruse et al. and withdrawal of the rejection is respectfully requested.

The Examiner maintains the rejection of claim 2 under 35 U.S.C. §103 as being obvious over Itokawa et al. or Naruse et al. combined with Horowitz et al. and the rejection of claims 8, 11 and 12 as being obvious over Itokawa et al. or Naruse et al. combined with Vater et al. Inasmuch as the invention encompassed by claim 1 is not obvious over Itokawa et al. or Naruse et al. dependent claims 2, 8 and 11 are similarly not obvious when the Itokawa et al. or Naruse et al. are combined with either Horowitz et al. or Vater et al. Withdrawal of the rejections is, therefore, respectfully requested.

It is believed that the claims, as they now stand, define patentable subject matter and as such a passage to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, Joe McKinney Muncy (Reg. No. 32,334), in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method of inactivating lipid-enveloped viruses in non-cell culture biological products, which comprises

providing a cyclic lipopeptide, a salt of the lipopeptide, an ester of the lipopeptide, or a mixture thereof;

contacting said product with the cyclic lipopeptide, salt of the lipopeptide, ester of the lipopeptide, or mixture thereof as an inactivating agent, at room temperature for 30 minutes up to 2 hours, wherein

the agent is added to said products at a concentration of 1-100 μM and an inactivation factor > 10^4 is achieved , wherein the agent directly inactivates any lipid-enveloped viruses present in said product.

10. (Twice Amended) The method according to claim 1 characterized in that one or more viruses selected from the group consisting of herpes viruses, human immunodeficiency virus type 1 (HIV-1), human immunodeficiency virus type 2 (HIV-2), simian immunodeficiency virus (SIV_{agm}), vesicular stomatitis virus (VSV), and Semliki-Forest virus (SFV) are inactivated.